Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
PWO-24649		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/005429	15.04.2004	22.04.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant		
ASTELLAS PHARMA INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005429

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-35 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 3-10,12-17 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1,2,11,18,19 received by this Authority on 22.12.2004

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005429

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 2,5,6,8,10

because:

☒ the said international application, or the said claims Nos. 2,5,6,8,10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claims 2, 5, 6, 8 and 10 include configurations that are related to methods for the treatment of the human body by means of therapy, and thus pertain to a subject matter for which this International Preliminary Examining Authority is not required to carry out an international preliminary examination under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 2,5,6,8,10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005429

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3, 4, 7, 9, 11-19	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1, 3, 4, 7, 9, 11-19	NO
Industrial applicability (IA)	Claims	1, 3, 4, 7, 9, 11-19	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: WO 02/100836 A2 (ACTIVE PASS PHARM. INC.), 19 December 2002, entire text; claims; page 43, line 14 to page 46, the last line; and the examples & US 2003/125338 A & US 2003/191144 A & EP 1399426 A2

Document 2: WO 02/28433 A2 (GLAXO GROUP LTD.), 11 April 2002, entire text; claims; page 3, lines 11 and 24 to 31; and pages 21 to 24 & AU 2001/92044 B & US 2004/29938 A & JP 2004-510749 A

Document 3: WO 99/4815 A1 (YAMANOUCHI PHARM. CO., LTD.), 04 February 1999, entire text; page 13, lines 4 and 5; and examples 1 and 2 & AU 98/83559 B & EP 1023907 A1

Document 4: JP 2001-354671 A (NIPPON CHEMIPHAR CO.), 25 December 2001, entire text; claim 11; page 28, column 53, lines 5 to 6; and example 10 & WO 01/79197 A1 & AU 2001/42747 B

Document 5: WO 03/16291 A1 (NIPPON CHEMIPHAR CO.), 27 February 2003, entire text; claim 18; page 32, lines 10 to 11; and examples 51 to 53

Document 6: WO 02/76957 A1 (NIPPON CHEMIPHAR CO.), 03 October 2002, entire text; page 17, lines 30

to 50; and example 3 & EP 1371650 A1 & AU 2002/232243 B

Document 7: J. M. PETERS et al., "Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor β(δ)," Mol. Cell. Biol., (2000), Vol. 20, No. 14, pages 5119 to 5128, entire text

Document 8: I. SALUJA et al., "PPAR δ agonists stimulate oligodendrocyte differentiation in tissue culture," Glia, (2001), Vol. 33, No. 3, pages 191 to 204, entire text

Document 9: S. BASU-MODAK et al., "Peroxisome proliferator-activated receptor β regulates acyl-CoA synthetase 2 in reaggregated rat brain cell cultures," J. Biol. Chem., (1999), Vol. 274, No. 50, pages 35881 to 35888, entire text

Document 10: JP 10-324626 A (Ono Pharmaceutical Co., Ltd.), 08 December 1998, entire text; claims 8 and 9; and paragraphs [0021] and [0035] & EP 632008 A1 & CA 2124784 A1 & JP 7-316092 A & JP 9-118644 A & JP 10-204023 A & US 6201021 A & US 2003/96802 A

Document 11: JP 2002-543124 A (Merck Patent GmbH.), 17 December 2002, entire text & WO 00/66110 A1 &. AU 2000/47481 B & EP 1185259 A1 & US 6395780 A

Document 12: WO 01/39779 A1 (UCB S.A.), 07 June 2001, entire text & AU 2001/15241 B & EP 1244456 A1 & JP 2003-515564 A

Document 13: JP 2002-539245 A (SYNCHRONEURON, LLC), 19

November 2002, entire text & WO 00/56301 A2 & AU 2000/38950 B & EP 1162960 A2 & US 6391922 A & US 2002/119912 A

Document 14: Megumi TAKAHASHI et al., "Shorei Hokoku Sodium Valproate ga Boryoku ni Yuko de atta Alzheimer-gata Chiho no 1 Rei," Brain and Nerve, (1996), Vol. 48, No. 8, pages 757 to 760, entire text

Document 15: A. LAMPEN et al., "New molecular bioassays for the estimation of the teratogenic potency of valproic acid derivatives in vitro: activation of the peroxisomal proliferator-activated receptor (PPAR δ)," Toxicol. Appl. Pharmacol., (1999), Vol. 160, No. 3, pages 238 to 249

[1]

Document 1 discloses the feature of employing compounds that exhibit a PPAR δ agonizing activity, which are capable of adjusting the production and the elimination of β-amyloids within cells, as effective components for the treatment of Alzheimer's disease.

Herein, Alzheimer's disease is one example of a neurodegenerative ailment that is associated with the "death of the cells of the central nervous system," as set forth in claim 16; furthermore, the fact that PPAR δ agonists are thought to play an important role in the production and the activation of the tissues of the nervous system (or the cells of the nervous system) by inducing the differentiation and the proliferation of glia cells and/or by controlling acyl-CoA synthetase 2, which is important for the metabolism of lipids in the

brain, etc., can be considered to have been well known prior to the priority date of the present application, as disclosed in documents 7 to 9. Therefore, it would have been easy for a person skilled in the art to conceive of administering the abovementioned compounds that are capable of controlling the production and the elimination of β-amyloids, which are disclosed in document 1, and/or the well-known PPAR δ agonist compounds that are presented in the examples thereof (page 13, line 30 to page 14, line 6), for example, in order to control the damage and the degeneration of the cells of the central nervous system and thereby ameliorate the effects of Alzheimer's disease.

Therefore, claim 16 does not involve an inventive step in the light of a combination of document 1 and documents 7 to 9.

[2]

Documents 2 to 6 make disclosures in relation to therapeutic agents for the central nervous system, which comprise a compound that exhibits a PPAR δ agonizing activity as the effective component for ameliorating ailments that are associated with the death of the cells of the central nervous system; in particular, the documents in question present Parkinson's disease, cerebral infarctions, cerebral haemorrhages and the like as examples of ailments which can be treated via the administration of the abovementioned therapeutic agents (refer to document 2 with regards to Parkinson's disease, and to document 3 with regards to cerebral infarctions and cerebral haemorrhages).

Therefore, claims 1, 3, 4, 7 and 11 to 16 do not

involve an inventive step in the light of any one of documents 2 to 6.

In addition, the fact that PPAR δ agonists are thought to play an important role in the production and the activation of the tissues of the nervous system (or the cells of the nervous system) by inducing the differentiation and the proliferation of glia cells and/or by controlling acyl-CoA synthetase 2, which is important for the metabolism of lipids in the brain, etc., can be considered to have been well known prior to the priority date of the present application, as disclosed in documents 7 to 9. Therefore, it would have been easy for a person skilled in the art to conceive of administering the PPAR δ agonist compounds that are disclosed in document 1 or documents 2 to 6 and/or other well-known PPAR δ agonist compounds such as the L-165041 or GW501516 compounds that are presented in the examples of the other documents, for example, in order to ameliorate the ailments that are set forth in claim 1, which are associated with the damage, the degeneration or the death of the cells of the central nervous system, in addition to the ailments that are presented in the examples of documents 2 to 6.

Therefore, claims 1, 3, 4, 7, 9 and 11 to 19 do not involve an inventive step in the light of a combination of document 1, any one of documents 2 to 6 and any one of documents 7 to 9.

However, if it were apparent from comparative examples or the like in which other PPAR δ agonists were administered in the same manner, for example, that the administration of either L-165041 or GW501516 as the PPAR δ agonist for ameliorating the ailments that are

specifically set forth in claim 1 would result in superior effects that could not have been predicted in the light of the cited documents, then it would be possible to establish that claims 9 and 17 involve an inventive step.

Documents 10 to 14 disclose the feature of employing a valproic acid or a salt thereof as the effective component in a therapeutic agent against various ailments that are related to the cells of the nervous system; in particular, the documents in question present external head wounds and Parkinson's disease examples of ailments which can be treated via the administration of the abovementioned therapeutic agents (refer to document 12 (claim 10, for example) with regards to external head wounds, and to document 13 with regards to Parkinson's disease).

Herein, the fact that valproic acids or salts thereof are PPAR δ agonists is considered to have been so well known prior to the priority date of the present application that it should not be necessary to refer to the disclosures of document 15, for example, in relation thereto. In addition, the fact that PPAR δ agonists are thought to play an important role in the production and the activation of the tissues of the nervous system (or the cells of the nervous system) by inducing the differentiation and the proliferation of glia cells and/or by controlling acyl-CoA synthetase 2, which is important for the metabolism of lipids in the brain, etc., can be considered to have been well known prior to the priority date of the present application, as disclosed in documents 7 to 9. Therefore, it would have been easy for a person skilled in the art to conceive of

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

administering the valproic acids or salts thereof that are disclosed in any of documents 10 to 14, for example, in order to ameliorate any of the ailments that are set forth in claim 1, which are associated with the damage or the degeneration of the cells of the central nervous system.

Therefore, claims 1, 3, 4, 7, 11 to 16, 18 and 19 do not involve an inventive step in the light of a combination of any one of documents 10 to 14, document 15 and any one of documents 7 to 9.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005429

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 03/33493 A1 [E,X/E,Y]	24.04.2003	09.10.2002	12.10.2001

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/005429

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

[1]

Claim 1 pertains to therapeutic agents against Parkinson's disease, cerebral infarctions, external head wounds, cerebral haemorrhages or damage to the spinal cord, which comprise a compound that is defined by means of a desired property, i. e. being a "PPAR δ agonist," as the active component. Therein, the scope of claim 1 includes any compound that exhibits such a property; however, only an extremely small portion of the claimed compounds can be considered to be supported in the description in the meaning of PCT Article 6, or to be disclosed therein in the meaning of PCT Article 5.

In addition, it is impossible to specify the scope of the compounds that exhibit the property of being a "PPAR δ agonist," even with consideration of common technical knowledge at the time the present application was filed. As a result, claim 1 does not conform to the requirement of clarity, as stipulated in PCT Article 6 (In the technical field pertaining to compounds, including medical compounds, it is generally difficult to predict the properties of a compound from only the chemical structure thereof; therefore, although one may indicate that there are a plurality of known compounds with a variety of different chemical structures which exhibit the property of being a "PPAR δ agonist," it can also be said to be impossible to clearly understand which of these known compounds correspond to the "PPAR δ agonists" in question and which of these known compounds do not correspond to the "PPAR δ agonists" in question in the light of only the indicated disclosures).

Box No. VIII Certain observations on the international application

Therefore, the opinion that is expressed in the present report was formed on the basis of the results from a search of the prior art that was primarily carried out in relation to the correlation between to the compounds that are set forth in claims 9 and 17 or other compounds that clearly exhibit a PPAR δ agonizing activity and the ameliorating actions thereof in relation to the ailments that are set forth in claim 1.

[2]

As is indicated in Box V, the feature of employing a PPAR δ agonist compound as the effective component for the treatment of ailments that are associated with the damage, the deterioration or the death of the cells of the central nervous system can be considered to have been well known prior to the priority date of the present application (for example, refer to the sections pertaining to documents 1, 2 to 6 and 10 to 14 in Box V); therefore, at the very least Parkinson's disease, cerebral infarctions, external head wounds, cerebral haemorrhages or damage to the spinal cord, which are set forth in claim 1 as examples of ailments which can be treated via the administration of a PPAR δ agonist compound, cannot be considered to be a group of ailments that have a special technical feature in common (other than the feature of being associated with the damage, the deterioration or the death of the cells of the central nervous system).

Furthermore, the ailments that are set forth in claim 1 include ailments such as "external head wounds," which exhibit symptoms that are not necessarily associated with the damage or the deterioration of the

Box No. VIII **Certain observations on the international application**

cells of the central or peripheral nervous systems. Therefore, at the time the present application was filed, it is thought that a person skilled in the art would not have considered all of the aforementioned ailments to be closely related by a common action mechanism or the like.

As a result, not all of the configurations involving combinations of the optional PPAR δ agonist compounds and the abovementioned ailments which set forth in claims 1 and 11, at least, can be said to have a special technical feature in common, even within each of the claims themselves; therefore, the inventions in question cannot be said to be so linked as to form a single general inventive concept.

In addition, claims 7, 14 and 15, like claims 1 and 11, also include flaws which are similar to those indicated above due to the fact that the PPAR δ agonist compounds and/or the ailments that can be treated via the administration of the PPAR δ agonist compounds are not specified in a sufficient manner.